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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,785	SZALAY ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18 and 20-22* is/are pending in the application.

4a) Of the above claim(s) *3-5,8,10,11,13 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,7,9,12,14,16,18 and 20-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :7/21/05,7/26/05,6/06,4/06,11/07,8/05,3/07,1/07,11/06,7/06.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 27 June 2005 as the US national stage of international application PCT/EP03/05907, which claims benefit of European patent application 02012552.2 filed 5 June 2002. The preliminary amendments filed 3 December 2004 and 26 October 2007 have been entered. Claims 1-19 were originally filed. Claims 1-19 were amended and claim 20 was added in the 3 December preliminary amendment. Claims 1-9, 12-16, 18 and 20 were amended, claims 17 and 19 were cancelled and claims 21 and 22 were added in the 26 October preliminary amendment. Claims 1-16, 18 and 20-22 are pending.

Election/Restrictions

Applicant's election with traverse of Group I and the species in which the detectable molecule is a protein that induces a signal detectable by magnetic resonance imaging (MRI), the microorganism or cell is a bacterium, the bacterium is E. coli, and the disease is an atherosclerotic disease in the reply filed 26 October 2007 is acknowledged. The traversal is on the ground(s) that the claims of Group II have been amended such that they are now within the scope if elected Group I.

The restriction requirement among the inventions identified in the 25 July 2007 Office Action is withdrawn. Upon consideration of the relevant art it is evident that the identified inventions are not patentably distinct. However, the requirement for election of species is maintained. Applicant does not present arguments traversing the requirement for species election.

The election of species requirement is still deemed proper and is therefore made FINAL.

Claims 3-5, 8, 10, 11, 13 and 15 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the 26 October reply.

Claims 1, 2, 6, 7, 9, 12, 14, 16, 18 and 20-22 are presently under consideration.

Claim Objections

Claim 1 is objected to because of the following informalities: The claim recites "wound" and "wounded tissue" of a subject as alternatives. However, there appears to be no difference between a wound and wounded tissue as used in the application. Therefore, the recitation of wound or wounded tissue is redundant. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6, 7, 9, 12, 14, 16, 18 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting a wound comprising administering a bacterial cell selected from *E. coli* and attenuated *S. typhimurium*, or attenuated *V. Cholerae* does not reasonably provide enablement for a method of detecting a wound or inflammation in a subject comprising administering any microorganism or cell to a

subject and detecting the accumulation of the microorganism or cell at a wound or inflamed tissue in the subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The instant claims are directed to a method comprising administering a microorganism or cell that is detectable in a subject and monitoring the subject to detect accumulation of the microorganism or cell at a wound, wounded tissue or inflamed tissue, whereby detection of the accumulation indicates the location of the wound, wounded tissue or inflamed tissue. The specification states, "Any microorganism or cell is useful for the diagnostic and therapeutic uses of the present invention, provided that it replicates in the organism, is not pathogenic for the organism e.g. attenuated and, is recognized by the immune system of the organism, etc." (Paragraph bridging pages 6-7.) And specifically suggests the use of bacteria, viruses and mammalian cells. (See originally filed claims 7 and 10.) Thus, the claims broadly encompass practicing the claimed method using any virus, any

bacterium or any mammalian cell having the capacity to accumulate at the location of any wound or any site of inflammation with sufficient specificity that the detectable accumulation of the microorganism can be used to indicate the location of a wounded or inflamed tissue.

Amount of direction provided by the inventor and existence of working examples: In support of the claimed invention, Applicant discloses that luminescent *S. typhimurim* and *V. cholera* injected into the femoral vein of nude mice and C57BU6J mice specifically accumulated at the site of cutaneous wounds. (Example 2, Figures 2-4.) It is noted, however, that the data presented (which consists of a single mouse for each condition) appear to show that the accumulation of bacteria depends on the strain of bacteria used, the location of the wound and the strain of mouse. For example, the nude mouse injected with *Salmonella* exhibits accumulation of bacteria at the leg wound and ear tag (Figure 2B), the nude mouse injected with *Vibrio* exhibits accumulation only at the leg wound (Figure 3B), while the immunocompetent mouse exhibits accumulation of *Vibrio* only at the ear tag (Figure 4). Thus, the working examples demonstrate that the accumulation of any given strain of bacteria at any given wound in any given animal is highly variable and unpredictable.

The application further teaches that when inflammation was induced at a rat aortic valve by implanting a catheter near the heart valve, intravenously injected light emitting *E. coli* were found to accumulate in the heart of catheterized animals but not control animals. (Example 3 and Figure 6.)

It is noted that the application presents no data at all with respect to microorganisms other than bacteria. With regard to the findings presented, the specification teaches, "In the experiments leading to the present invention it has been found that inflamed tissues, e.g. near

implanted material, permit bacterial colonization." (Paragraph bridging pages 3-4.) The application then goes on to assert that the finding that tissues that are irritated by implanted materials are more susceptible to bacterial colonization "open the way for (a) designing multifunctional viral vectors useful for the detection of wounded or inflamed tissue based on signals like light emission or signals that can be visualized by MRI and (b) the development of bacterium- and mammalian cell-based wounded or inflamed tissue targeting systems..." (Paragraph bridging pages 4-5; emphasis added.)

Thus, the application demonstrates that some strains of bacteria will colonize areas in which foreign bodies have been implanted and seeks to claim using any virus, any bacterium or any mammalian cell having the capacity to accumulate at the location of any wound or any site of inflammation with sufficient specificity that the detectable accumulation of the microorganism can be used to indicate the location of wounded or inflamed tissue. At the same time, the application acknowledges that what is demonstrated merely "opens the way for" designing viral vectors useful for detection of wounded or inflamed tissue and development of bacterium- and mammalian cell-based wounded or inflamed tissue targeting systems.

With regard to actually practicing the claimed method using a virus or mammalian cell, the application provides no specific guidance such as which types of virus or mammalian cells have the same properties as the bacteria used in the working examples with respect to the ability to specifically accumulate at the site of an irritant. Instead the application merely asserts that viruses such as *Vaccinia* virus, AAV, retrovirus, etc. and mammalian cells such as a stem cell are useful for the diagnostic and therapeutic uses of the invention (first and second paragraphs on

page 11) without providing any basis for concluding that these viruses and cells could actually be used in the claimed method.

With regard to accumulation of any microorganism at sites of inflammation other than wounds or tissue into which a foreign object has been introduced, e.g., an atherosclerotic lesion, the application refers to reports providing evidence that *C. Pneumonia, H. pylori,* CMV and HSV have been found in atherosclerotic plaques and speculates that intravenously administered microorganisms and cells will penetrate into atherosclerotic plaques where they will replicate to a sufficient degree that they will be capable of indicating the presence of a plaque. (See especially the paragraph bridging pages 13-14.) However, no evidence is presented to indicate that any intravenously administered microorganism or cell would be capable of selective accumulation within an atherosclerotic lesion such that it could actually be used to identify the location of the lesion as claimed.

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The physiological art is recognized as unpredictable. (MPEP 2164.03.) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides

broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

In addition to the general unpredictability of the physiological arts, the unpredictability of the art related to the instant invention is clearly evidenced by the teachings of the instant application. In the paragraph bridging pages 1-2, the specification teaches (emphasis added):

> Bacteremias may arise from traumatic injuries and surgical procedures as well as from physiological functions…A potential consequence of bacteremia is colonization of susceptible sites. However, despite the occurrence of transient bacteremias, only a certain percentage of high-risk patients develop bacterial colonization of potentially susceptible sites. A number of investigators have suggested that bacteria from the blood circulation can colonize inflamed tissues in animal models and on the surface of implanted materials. The inconsistency in the pathological changes in humans following a bacteremia may also be due to the resistance of host immune system, the variability in the concentration of bacteria in the blood subsequent to different bacteremia events, and the virulence of any given bacterial strain.

Thus, the application teaches that the colonization of potentially susceptible sites by any given bacterium is variable and might be dependent on the properties of the host, the amount of bacteria present and the properties of the bacterial strain. This variability is also evidenced by the working examples, which show that different wounds were colonized depending upon the bacterial strain injected and the mouse strain used in the experiment.

In addition, Yu et al. (2003) *Anal. Bioanal. Chem.* 377: 964-72 (made of record in the IDS filed 21 July 2005), Applicant's own publication, provides a recent review of the art

evidencing the nascent state thereof and the unpredictability of achieving the breadth of the claimed invention. With regard to bacterial cells, Yu teaches a few species of bacteria which appear to preferentially colonize cancerous tissues, but the mechanism of such colonization, while proposed to be due to various things, is not yet elucidated (pp. 966-67). Moreover, a particular mouse was found that showed a very short term accumulation of bacteria which disappeared prior to full disappearance of the bacteria in a particular mouse strain (p. 966). Further, Yu discloses that administration-type-dependent colonization is common, but there appears to be no reasoning to predict which administration will yield which colonization type (p. 966, paragraph bridging columns).

With regard to detecting areas of inflammation such as atherosclerosis, the art does not provide any guidance as to how one would detect atherosclerotic plaques as claimed. It is further noted that recent reviews of art recognized animal models of atherosclerotic disease do not mention the animal models used in the instant working examples. (See, Jawien et al. (2004) *J. Physiol. Pharmacol.* 55:503-517 and MacMahon et al. (2005) *Curr. Drug Targets* 5:433-440).

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to make and use the full scope of what is presently claimed without undue experimentation. The instant application demonstrates that some strains of bacteria will colonize areas in which foreign bodies have been implanted and seeks to claim using any virus, any bacterium or any mammalian cell having the capacity to accumulate at the location of any wound or any site of inflammation with sufficient specificity that the detectable accumulation of the microorganism can be used to indicate the location of wounded or inflamed tissue. However, as

described above, the instant application and applicant's own teachings in the non-patent literature evidence the nascent state of the relevant art even with respect to bacteria. Given this unpredictability, the skilled artisan seeking to make and use the full scope of the invention as claimed would be forced to determine experimentally which embodiments within the expansive scope of the claims would be operative (i.e., which microorganism will accumulate at a wound or any given site of inflammation to a degree that the accumulation can be used to indicate the location of the wound or inflamed tissue).

With regard to the use of microorganisms other than bacteria in the claimed method, the disclosure amounts to no more than the presentation of an idea with no specific disclosure as to how that idea is to be carried out. As stated in the application, the disclosure opens the way for designing multifunctional viral vectors useful for the detection of wounded or inflamed tissue based on signals like light emission or signals that can be visualized by MRI and the development of bacterium- and mammalian cell-based wounded or inflamed tissue targeting systems..."

"It must be remembered, however, that '[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling disclosure.' *Genentech*, 108 F.3d at 1366 (quoting *Brenner v. Manson*, 383 U.S. 519, 536 [148 USPQ 689] (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion')). Thus, while the need for some experimentation is by no means necessarily fatal, 'reasonable detail must be

provided in order to enable members of the public to understand and carry out the invention.' Id." *University of Rochester v. G.D. Searle & Co.*, 68 USPQ2d 1424 (DC WNY 2003).

In view of the foregoing, the skilled artisan would not be able to practice the invention presently claimed in accordance with its full scope without having to engage in undue experimentation to extend the knowledge available in the application and the prior art such that the method could be practiced using any virus, any bacterium or any mammalian cell having the capacity to accumulate at the location of any wound or any site of inflammation with sufficient specificity that the detectable accumulation of the microorganism can be used to indicate the location of wounded or inflamed tissue as encompassed by the claims. Therefore, the claims are properly rejected under 35 USC § 112, first paragraph, as lacking an enabling disclosure.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 6, 7, 9, 12, 14, 16, 18 and 20-22 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-35, 39, 45, 46, 51, 52, 54, 55, 64, 65, 67-72, 74, 75, 77 and 78 of copending Application No. 10/849,644. Although the conflicting claims are not identical, they are not patentably distinct from each other because they either anticipate the claims of the instant application or the invention claimed in the instant application is an obvious variation of an embodiment disclosed in the patent which provides support for the conflicting claim.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would be obvious over, the reference claim(s). The MPEP states, at §804,

> The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. *In re Boylan*, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in *Vogel* recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 103, since only the disclosure of the invention claimed in the patent may be examined."

In the instant case, independent claim 33 of the '664 application is directed to a method for detecting the presence of wounded or inflamed tissue comprising administering a bacterium

encoding a detectable protein that induces a detectable signal, monitoring the subject to detect the detectable protein or signal to detect accumulation of the bacterium at any wounded or inflamed tissue, wherein the subject is one who is being evaluated for the presence or absence of wounded or inflamed tissue, the bacterium is non-pathogenic or attenuated, the bacterium is recognized by the immune system of the subject, and the bacterium replicates in the subject.

The instant claims 1, 7, and 20 are wholly generic to all that is recited in independent claim 33, and claims 34-35, 39, 45, 46, 51, 52, 54, 55, 64, 65, 67-72, 74, 75, 77 and 78 which depend therefrom, and are therefore anticipated by the claims of the '644 application. Furthermore, the instant claims 6 and 16 are anticipated by claims 64 and 65 of the '644 application, and the instant claim 9 is anticipated by claims 51, 52, 54 and 55 of the '644 application. With regard to the instant claims 2, 12, 14, 18 and 21, which recite that the microorganism or cell encodes a protein for the therapy of a wounded or inflamed tissue, wherein the protein includes a lipase, protease, lysozyme, propapoptotic factor and PPAR-agonist and the promoter might be inducible, each of these embodiments are disclosed in the portions of the '644 application specification that provide support for the invention claimed therein. (See, e.g., paragraphs 0025-0026 and 0043.) Likewise, paragraph 0049 of the '644 specification discloses an embodiment of the claimed invention which further comprises administering a therapeutic agent as recited in the instant claim 22. As a substantial portion of the disclosure of the '644 application teaches the embodiments claimed in the instant application, one of ordinary skill in the art would conclude that those embodiments are obvious variants of what is claimed in the '644 application. Therefore, the claims are properly rejected under the judicially created doctrine of obviousness type double patenting.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102[1]

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 6, 12, 14, 18 and 20-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Costa et al. (2001) *J. Immunol.* 167:2379-2387 (made of record in the IDS filed 8 November 2007) as evidenced by Wade et al. 2006: *Am. J. Respir. Cell Mol. Biol.* 34:727-737 and Weissleder et al. (2001) *Radiol.* 219:316-333.

The claims are directed to a method administering a microorganism or cell to a subject, wherein the microorganism or cell is detectable in the subject; and monitoring the subject to detect the accumulation of the microorganism or cell at a wounded or inflamed tissue in the subject, whereby, detection of the accumulation indicates the location of the wound, wounded tissue or inflamed tissue.

The section entitled, "*MBP-specific transduced CD4$^+$ T cells traffic to the CNS*" Costa et al. teaches a method wherein MBP-specific CD4$^+$ T cells transduced with a GFP-luciferase reporter gene were infused into MBP-immunized recipient mice and the mice were monitored for

[1] It is noted that, although the prior art teaches some enabled embodiments within the scope of the generic claims, these species, like those of the instant application, are not enabling for the full scope of what is presently claimed. Therefore, the art rejections in no way contradict the conclusion of lack of enablement under 35 USC § 112, first paragraph.

accumulation of fluorescent cells in the inflamed regions of the CNS. The method of Costa et al. comprises all of the elements of the instant independent claim 1. Furthermore, the cells are not pathogenic to the subject (as evidenced by the absence of pathology in the control mice) and are recognized by the immune system of the subject (i.e., T cells are recognized by various other components of the immune system). Thus, the method also anticipates the instant claim 20.

The instant claims 2, 6, 12, 14, 18 and 21 are directed to the method of claim 1, wherein the cell encodes a protein for the therapy of a wounded or inflamed tissue or a disease associated therewith or a protein that induces a signal detectable by MRI. The claims, as written, require only that the cell comprise a nucleic acid that encodes a protein that could be used in the therapy of a wounded or inflamed tissue or induces a signal detectable by MRI. As the genome of the mammalian cell used in the method of Costa et al. would comprise genes encoding proteins having each of the activities recited in claim 21 (e.g., a lipoprotein lipase), the method of Costa et al. meets the limitations of the instant claims 2, 12, 14 and 21. In addition, Wade et al. evidences that expression of the mammalian lipoprotein lipase gene can be induced by dexamethasone/8-Br-cAMP/isobutylmethylxanthine. (See especially Table 2 and the caption thereto.) Thus, at least one of the proteins encoded by the cells is under the control of an inducible promoter according to the limitations of claim 18. Likewise, Weissleder et al. evidences that proteins encoded in the mammalian genome such as cytosine deaminase, tyrosinase, arginine kinase, creatinine kinase and transferrin induce a signal detectable by MRI. (See especially Table 2 and the caption thereto.) Thus, the cells of Costa et al. encode proteins that induce a signal detectable by MRI and the method of Costa et al. comprises all of the limitations of the instant claim 6.

Finally, the instant claim 22 is directed to the method of claim 1, further comprising administering a therapeutic agent for therapy of an inflamed tissue or disease associated therewith. In the second full paragraph on page 2384, Costa et al. teaches the method wherein cells labeled with yellow fluorescent protein (YFP) are introduced, which cells also express the therapeutic protein IL-12, and the animal is monitored for the accumulation of the YFP labeled cells in the brain and spinal cord. The method of Costa et al. comprises all of the elements of the instant claim 22.

Costa et al. teaches a method comprising each of the limitations of the instant claims. Therefore, the claims are anticipated by the prior art.

Claims 1, 7, 9 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Hamblin et al. (20012) Photochem. Photobiol. 75:51-57 (made of record in the IDs filed 18 April 2006).

The limitations of the instant claim 1 are described herein above. Hamblin et al. teaches a method comprising administering a bioluminescent strain of *E. coli* DH5α to a mouse and monitoring the mouse for accumulation of the bacteria at a wound (see especially the discussion of *in vivo* studies beginning at the bottom of page 53, Figures 2 and 3 and the captions thereto), whereby the accumulation of the bacterium at a wound evidences the continued presence of the wound, as Hamblin et al. teaches that the nutrients and moisture provided by the wound are required for maintenance of the bacterial infection (see page 54, lines 4-13). The method of

[2] Posted on the world wide web November 2001. See the first footnote on page 51.

Hamblin et al. comprises all of the elements required by the method of the instant claim 1. In addition, the microorganism of Hamblin et al. is an attenuated strain of *E. coli*, which Hamblin et al. teaches replicates in the mouse but is self-limiting and not pathogenic. (See especially page 54, lines 13-16.) Thus, the method of Hamblin et al. also anticipates the limitations of claims 7, 9 and 20 of the instant application.

Hamblin et al. teaches a method comprising each of the limitations of the instant claims. Therefore, the claims are anticipated by the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Costa et al. (*supra*), as applied to claim 1 herein above, in view of Weissleder et al. (*supra*).

Claim 16 is directed to the method of claim 1 wherein monitoring is performed by MRI. As described above, Costa et al. teaches a method comprising all of the elements of the instant claim 1 wherein monitoring is performed by fluorescence imaging. Costa et al. fails to teach the method wherein the monitoring is performed by MRI.

Weissleder et al. teaches that MRI imaging using proteins such as transferrin was known in the art as an alternative to optical imaging as used in the method of Costa et al. (See especially Table 2 and the section entitled "MR Imaging" beginning on page 322.) Weissleder et al. further teaches that MRI provides the advantages of high spatial resolution and the ability to extract more than one measurement parameter at a given imaging session. Thus, one would be motivated to substitute the MR imaging as taught by Weissleder et al. for the optical imaging used in the method Costa et al. according to the requirements of the instant claim 16. Given the high level of skill in the art evidenced by the highly technical nature of the cited publications, one of ordinary skill in the art would have a reasonable expectation of success in practicing the method using MRI because doing so would require only the substitution of a MRI detectable protein (e.g., transferrin) for the fluorescent molecule used by Costa et al. and the use of standard MRI technology.

In addition, In *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the Supreme Court particularly emphasized "the need for caution in granting a patent based on a combination of elements found in the prior art," (*Id.* At 1395) and discussed circumstances in which a patent might be determined to be obvious. Importantly, the Supreme Court reaffirmed principles based on it precedent that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." (*Id.* At

1395.) In the instant case, the prior art differs from the claimed invention only in the substitution of one detection modality (i.e., optical imaging) for another modality known in the art (i.e., MRI). However, one of skill in the art could have substituted MRI for optical imaging and the result of the substitution would have predictably resulted in an effective method of locating labeled cells at an area of inflammation. Therefore, the claimed invention, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made.

In view of the foregoing, the claim is properly rejected under 35 USC § 103(a) as obvious over the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel M Sullivan/
Primary Examiner
Art Unit 1636